Stereochemical Features of the Anomerizations in the 5,6-Dihydrothymine Nucleoside Series

Jasenka Matulić-Adamić, Maja Pavela-Vrančič, and Vinko Škarić *
Laboratory of Stereochemistry and Natural Products, 'Ruder Bošković' Institute, 41001 Zagreb, Croatia, Yugoslavia

The transformation of (5*S*)-1-(3,5-anhydro-2-deoxy-β- (**1**) or α- (**4**) -D-*threo*-pentofuranosyl)-5,6-dihydrothymine by sodium iodide in acetic acid–butan-2-one gave the same mixture of (5*S*)-1-(2,5-dideoxy-5-iodo-β- (**2**) and α- (**3**) -D-*threo*-pentofuranosyl)-5,6-dihydrothymine in a ratio of 1:2. The intramolecular cyclization of the anomers (**2**) and (**3**) by silver acetate in methanol afforded the respective (5*S*)-1-(3,5-anhydro-2-deoxy-β- (**1**) and α- (**4**) -D-*threo*-pentofuranosyl)-5,6-dihydrothymine. The reductive dehalogenation of (**2**) and (**3**) led to (5*S*)-1-(2,5-dideoxy-β- (**5**) and α- (**6**) -D-*threo*-pentofuranosyl)-5,6-dihydrothymine, respectively. Treatment of the β-3′,5′-anhydro structure (**1**) with the strong acidic cation-exchange resin gave mainly the α-anomer (**4**). Some correlations of the stereoelectronic features with the anomerizations in the 2′-deoxy-D-*threo*- and *erythro*-pentofuranosyl series are indicated.

In a recent communication,[1] we have reported the stereoselective transformations of the thymidine derivatives by hydrogenation in the presence of 5% Rh/Al_2O_3. Thus, thymidine as well as the 3′,5′-anhydro- and 3′-deoxy- derivatives in the thymine nucleoside series gave the corresponding (5*S*)-5,6-dihydrothymine diastereoisomers. Our interest in diastereoisomeric differentiations of the 5-substituted pyrimidine nucleosides[2] has grown with the possible exploration of their biological activity[3] and awareness of their natural occurrence.[4,5] We also studied the stereochemical transformations of the 5,6-dihydrouridine derivatives at the sugar moieties[6] and the synthesis of the new heterocyclic compounds by the ring opening of the 5,6-uracil-1-yl part of the respective molecules.[7,8] In extension of these studies, we have now focussed our attention on the anomerization processes of the 5,6-dihydrothymine nucleosides with respect to their structural features and reaction media.

Results and Discussion

In contrast to the nucleophilic reactions of the aromatic 3′,5′-anhydro nucleosides[9] which gave the 5′-substituted derivatives arising from the cleavage of the respective oxetane ring system, (5*S*)-1-(3,5-anhydro-2-deoxy-β-D-*threo*-pentofuranosyl)-5,6-dihydrothymine[1] (**1**) on reaction with sodium iodide in acetic acid–butan-2-one (Scheme 1, pathway i) yielded two iodo compounds: 25% (R_F 0.37) and 46% (R_F 0.28).

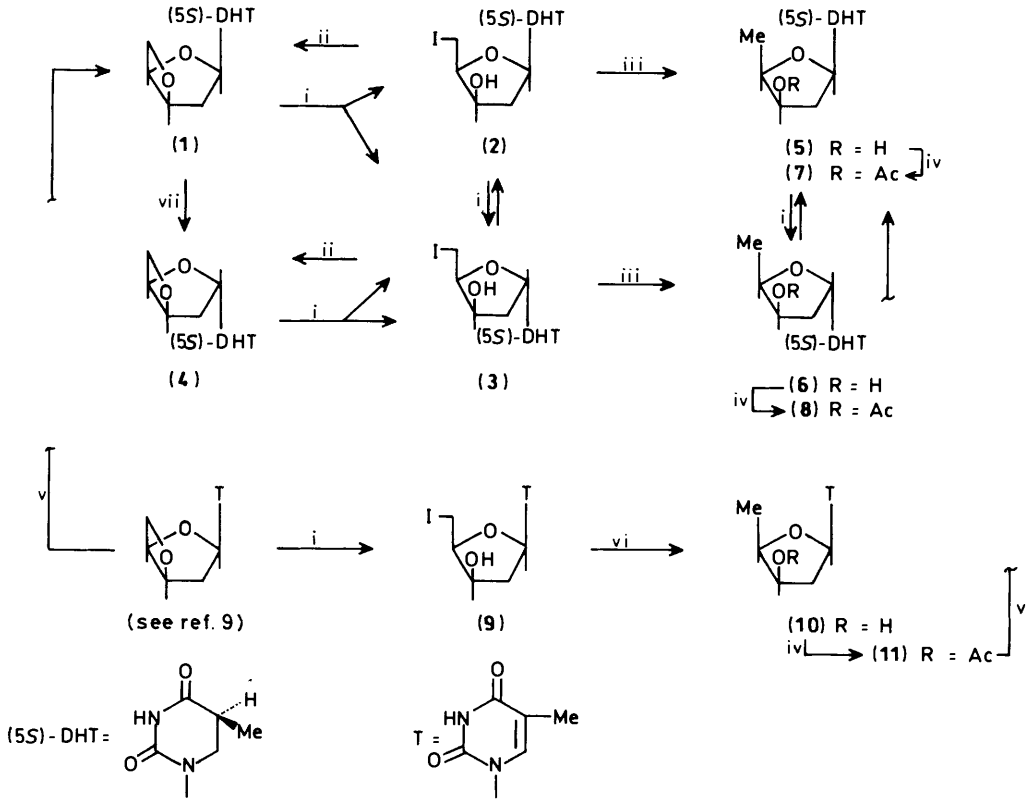
Structural assignments of these iodo compounds were effected on the basis of their elemental analyses, ^1H and ^{13}C n.m.r. spectra (see Experimental section and Table). Whereas the minor component, (5*S*)-1-(2,5-dideoxy-5-iodo-β-D-*threo*-pentofuranosyl)-5,6-dihydrothymine (**2**), R_F 0.37, exhibited in its ^1H n.m.r. spectrum resonances at δ 6.02 attributable to 1′-H, the major component, (5*S*)-1-(2,5-dideoxy-5-iodo-α-D-*threo*-pentofuranosyl)-5,6-dihydrothymine (**3**), R_F 0.28, showed the signal for the corresponding proton at δ 6.19. The ^{13}C n.m.r. spectrum of the β-5′-iodo- (**3**) and α-5′-iodo- (**3**) anomer showed a characteristic upfield shift[10] for C(5′) (δ 3.1 and 3.6 p.p.m., respectively).

In view of the relative ease of cleavage of the aromatic 3′,5′-anhydro nucleosides at the oxetane ring by nucleophilic attack at C(5′), we tested similar structures of the 5,6-dihydrothymine nucleosides. Thus, the nucleophilic reaction of the 3′,5′-anhydro compound (**1**) with sodium iodide under acidic conditions has been shown to proceed to the 5′-iodo compounds (**2**) and (**3**) by stereoselectively assisted anomerization. This accompanying anomerization would thus be a convenient route to the stereoselective synthesis of hitherto unknown α-nucleoside derivatives. In order to check such syntheses for the D-2′-deoxy-*threo*-pentofuranosyl series, the β-5′-iodo anomer

Table. ^{13}C N.m.r. chemical shifts (δ/p.p.m.) of the anomeric (5*S*)-5,6-dihydrothymine deoxynucleoside derivatives[a]

Compound	C-4,s	C-2,s	C-4′,d	C-1′-d	C-3′,d	C-5′,t	C-6′,t	C-2′,t	C-5,d	CH_3-4′,q	CH_3-5,q
(**1**)	173.0	153.6	88.9	86.9	79.1	75.3	42.3	37.4	35.5		12.8
(**4**)	172.6	152.5	86.6	84.8	77.8	76.5	42.5	34.8[b]	35.4[b]		12.3
(**2**)[c]	173.4	152.9	82.7	82.1	69.0	3.1	*d*	*d*	34.7		12.6
(**3**)[c]	172.8	152.3	84.3	82.9	70.3	3.6	*d*	*d*	34.7		12.2
(**5**)	173.1	152.8	84.8	78.5	71.8		44.5	39.8	35.7	13.7	13.0
(**6**)[c]	172.8	152.2	83.1	78.9	71.5		*d*	*d*	34.5	14.8	12.2
(**7**)[e]	172.8	152.8	82.5	76.8	73.9		42.2	37.3	35.5	13.9	13.0
(**8**)[c]	172.4	152.3	84.5	78.2	75.0		43.0	35.7[b]	35.3[b]	14.8	12.4
(**12**)[e]	172.6	153.1	83.7	80.5	74.2	63.9	42.0	34.0	35.3		13.0
(**13**)[e]	172.5	152.3	84.8	82.0	74.4	64.2	42.3	35.3[b]	35.4[b]		12.5
(**14**)[c]	173.1	152.9	83.7[b]	83.2[b]	73.1	8.8	41.8	35.7	34.7		12.7
(**15**)[c]	173.2	152.5	84.3[b]	83.3[b]	73.3	9.7	41.9	36.5	34.8		12.5

[a] In $CDCl_3$ unless otherwise stated. [b] Assignment could be reversed. [c] In $[^2H_6]Me_2SO$. [d] Obscured by those of Me_2SO. [e] CO of Ac at 170.5—169.9 p.p.m. and that of Me at 20.95—20.8 p.p.m.

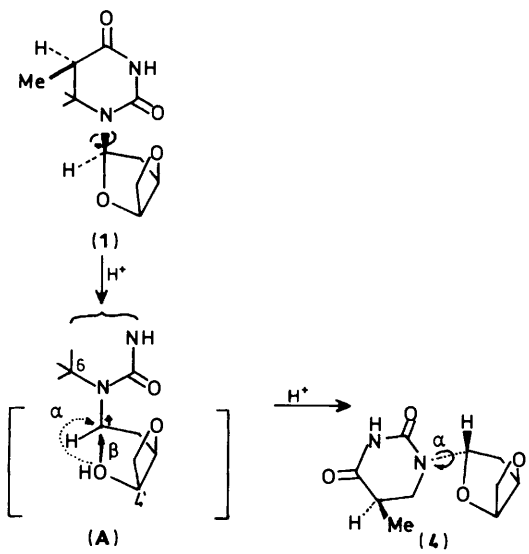


Scheme 1. *Reagents and conditions*: i, NaI–MeCOEt–AcOH; ii, AgOAc–MeOH; iii, H_2–10% Pd/C in 50% EtOH; iv, Ac_2O–py; v, H_2–5% Rh/Al_2O_3 in 50% EtOH; vi, H_2–5% Pd/C in 1M NaOH–EtOH; vii, Amberlite IR-120(H^+)–H_2O

(**2**) and its α-anomer (**3**) were independently treated under the same reaction conditions as were used for the regiospecific iodination of the 3′,5′-anhydro dihydro compound (**1**). Interestingly, both anomers gave within 2 h, the same mixture of compounds (**2**) and (**3**) in a ratio of 1:2. It should be noted that (**2**) and (**3**) proved to be inert when treated in the absence of sodium iodide. As expected, treatment of (5*S*)-1-(3,5-anhydro-2-deoxy-α-D-*threo*-pentofuranosyl)-5,6-dihydrothymine (**4**) (*vide infra*) with sodium iodide–acetic acid in butan-2-one resulted also in a mixture of compounds (**2**) and (**3**) in a ratio of 1:2. On the assumption that these experimental facts are unambiguously interconnected, simple explanations emerged. The anomerization processes proceeded independently to nucleophilic substitution at C(5′). On the other hand, the thermodynamic equilibrium between the α- and β- form appeared to be dependent on the substitution pattern at C(5′).

We next confirmed that the reaction of the 5′-iodo β-anomer (**2**) with silver acetate in MeOH (Scheme 1) gives the (5*S*)-β-3′,5′-anhydro compound (**1**). The α-5′-iodo anomer (**3**) when subjected to identical reaction conditions afforded (5*S*)-1-(3,5-anhydro-2-deoxy-α-D-*threo*-pentofuranosyl)-5,6-dihydrothymine (**4**). The diastereoisomeric purity of each of the cyclic products (**1**) and (**4**) so obtained was established by their singular ^1H and ^{13}C n.m.r. spectral signals. In particular, the interactions of the oxetane ring oxygen lone-pair with the C-6 protons (Scheme 2) by proximity (β-anomer) and steric decompression (α-anomer), substantially attributed to their respective chemical shifts. Thus, 6-H_a/H_b gave rise to signals at: δ 3.99/3.40 for (**1**) and 3.49/3.04 for (**4**).

In conjunction with our previous studies,[11] but avoiding basic conditions, we envisaged that stereochemically controlled dehalogenation of the β-5′-iodo- (**2**) and α-5′-iodo- (**3**) anomers would give the corresponding (5*S*)-1-(2,5-dideoxy-β- (**5**) and



Scheme 2.

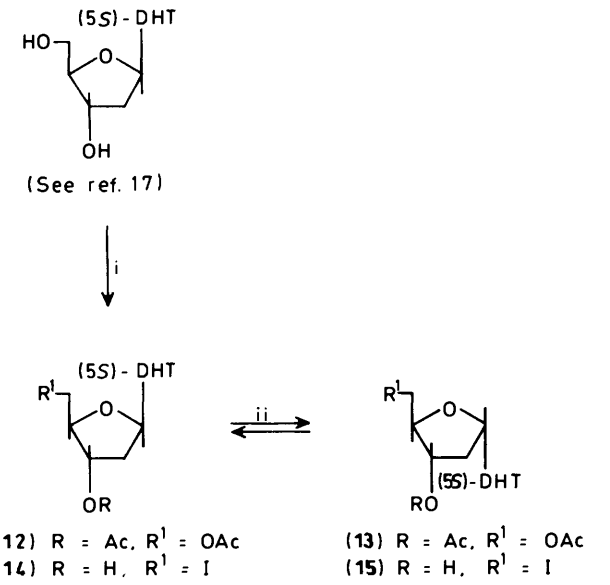
α-(**6**)-D-*threo*-pentofuranosyl)-5,6-dihydrothymines (Scheme 1) (see Experimental section). In contrast to earlier findings, reactions under basic conditions caused epimerization[1] at C-5. The β-4′-methyl- (**5**), $[\alpha]_D^{27}$ −56.5°, and α-4′-methyl- (**6**), $[\alpha]_D^{27}$ +4, anomers, gave rise to a doublet each centred, respectively, at δ 1.31 and 1.09. Acetylation of these compounds gave (5*S*)-1-(3-*O*-acetyl-2,5-dideoxy-β- (**7**) and α- (**8**) -D-*threo*-pentofuranosyl)-5,6-dihydrothymine, respectively (Scheme 1). The β-anomer (**7**) was independently prepared by stereoselective

5% Rh/Al_2O_3 hydrogenation of 1-(3-*O*-acetyl-2,5-dideoxy-β-D-*threo*-pentofuranosyl)thymine (**11**). The latter was obtained from 1-(2,5-dideoxy-5-iodo-β-D-*threo*-pentofuranosyl)thymine (**9**),[12] being reductively dehalogenated under basic conditions into the 5′-deoxy compound (**10**) and then acetylated. The preparation of compound (**9**) from the 3′,5′-anhydro structure followed the procedure described by Horwitz *et al.*[13]

It is known from the literature that the furanosyl nucleosides undergo rapid acid-catalysed isomerization to their more stable pyranosyl forms.[14,15] Systematic investigations by Seela *et al.*,[16] indicated that proton-catalysed nucleoside furanoside–pyranoside isomerizations were influenced by the aromatic nucleobase and sugar structure. As expected, the substituted 5′-hydroxy group, as present in the 3′,5′-anhydro- (**1**) and (**4**), 5′-iodo- (**2**) and (**3**), and 5′-deoxy- (**8**) and (**11**) structures prevent isomerizations to the pyranosyl forms. It is also interesting to note that the β-3′-*O*-acetyl-5′-deoxy compound (**7**) on treatment with the strong acidic cation-exchange resin IR-120 (H^+) caused only a 27% anomerization. No anomerization occurred with weaker reagents [benzoic acid, weak acidic cation-exchange resin IRC-50 (H^+)].

(5*S*)-1-(3,5-Anhydro-2-deoxy-β-D-*threo*-pentofuranosyl)-5,6-dihydrothymine (**1**) when treated with the strong acidic cation-exchange resin IR-120 (H^+) gave, within 2 h, 85% of the α-anomer (**4**). Steric and coulombic repulsions on the β-side of the carbocationic intermediate [**A**] (Scheme 2), in particular at the ureido segment because of the bulkiness of the oxetane ring system, may be responsible for the dislocation of the (**1**) $\rightleftharpoons$ (**4**) equilibrium in favour of (**4**) and preferred attack of the 4′-oxyanion upon the 'down' side. It should be added that the D-*threo*-pentofuranosyl-5,6-dihydrothymine structures here reported showed relative stability at the N-glycosidic bond in these acid-promoted rearrangements.

With sodium iodide–acetic acid (5*S*)-1-(3,5-di-*O*-acetyl-2-deoxy-β-D-*erythro*-pentofuranosyl)-5,6-dihydrothymine (**12**) (Scheme 3), prepared from (5*S*)-1-(2-deoxy-β-D-*erythro*-pentofuranosyl)-5,6-dihydrothymine,[17] generated a mixture of β- (**12**) and α- (**13**) anomers in a ratio of 1.7:1. For comparison, (5*S*)-1-(3,5-di-*O*-acetyl-2-deoxy-α-D-*erythro*-pentofuranosyl)-5,6-dihydrothymine (**13**) was also treated with sodium iodide–acetic acid and gave the same ratio of β- (**12**) and α- (**13**) anomers, whose analytical data were identical with those obtained from the anomer (**12**). This led to the conclusion that, being protected, formation of the anomers (**12**) and (**13**), followed a similar route to that of the aforementioned acetyl derivative (**7**) in the *threo* series.



Scheme 3. *Reagents and conditions:* i, Ac_2O–py; ii, NaI–MeCOEt–AcOH

It should be pointed out that if (5*S*)-1-(2,5-dideoxy-5-iodo-β-D-*erythro*-pentofuranosyl)-5,6-dihydrothymine[1] (**14**) was treated with sodium iodide–acetic acid the β- (**14**): α-(**15**) anomer ratio (1.5:1) was the reverse of that for the 5′-iodo anomers (**2**) and (**3**) in the *threo* series. This led to the conclusion that the 'up' oriented 3′-OH in the *threo* series, being unprotected [compounds (**2**) and (**3**)] could hinder rotation of the carbocationic intermediate at $^+C(1')$–N(1), particularly at a position close to the ureido segment (Scheme 2), and thus lower the yield of the β-anomer (**2**). This is not the case in the *erythro* series where the 3′-OH is 'down' oriented [compounds (**14**) and (**15**)].

Comparisons between the 2′-deoxy-*threo* and -*erythro* series, based on the above described experiments, showed direct correlations of their stereoelectronic features with the anomerization processes. However, with further work on the scope and limitations of this methodology using modified hydronucleosides, and in particular on those containing a variety of the 2′- and 3′-substituents, our understanding of the mechanisms involved in the anomerization processes should be enhanced. Anomerizations of modified 5,6-dihydrothymine nucleosides as well as of 1-(β-D-*erythro*-pentofuranosyl)-5,6-dihydrouracil, 1-(2,3,5-tri-*O*-acetyl-β-D-*erythro*-pentofuranosyl)-5,6-dihydrouracil, and 1-(β-D-arabinofuranosyl)-5,6-dihydrouracil are, therefore, currently being studied.

Experimental

M.p.s, uncorrected, were determined on a Kofler hot-stage apparatus. I.r. spectra were obtained for KCl pellets on a Perkin-Elmer 297 spectrophotometer. U.v. spectra were taken for solutions in ethanol on a Perkin-Elmer double-beam spectrophotometer model 124. ^1H N.m.r. spectra were recorded for solutions in $CDCl_3$ on a JEOL FX90Q spectrometer operating at 89.55 MHz with tetramethylsilane as the internal standard unless otherwise stated. ^{13}C N.m.r. spectra were determined for solutions in $CDCl_3$ on a JEOL FX90Q spectrometer operating at 22.5 MHz unless otherwise stated. Multiplicities s, d, t, and q refer to off-resonance decoupled spectra. Optical rotations were determined on a Zeiss-Winkel 179707 apparatus. The silica gel (Merck, ASTM; 70—230 mesh) was used for column chromatography. The silica gel (Merck HF_{254}, type 60) which was used for t.l.c. was activated at 110 °C for 60 min. The products were located by exposure to iodine vapour and by u.v. illumination. R_F Values were measured by developments in CH_2Cl_2–MeOH (20:1).

Transformations of (5S)-1-(3,5-*Anhydro*-2-*deoxy*-β-D-threo-*pentofuranosyl*)-5,6-*dihydrothymine*[1] (**1**) *into the Anomeric* (5S)-5′-*Iodo Derivatives* (**2**) *and* (**3**).—A solution of the β-3′,5′-anhydro compound (**1**) (734 mg, 3.24 mmol) in butan-2-one (19 ml) and acetic acid (4 ml) was heated with sodium iodide (1.44 g, 9.60 mmol) under reflux for 16 h. The solvent was evaporated and the residue co-evaporated with ethanol several times under reduced pressure. The residue was partitioned between CH_2Cl_2 and 5% aqueous sodium thiosulphate. The extract was washed with water, dried (Na_2SO_4), and evaporated to dryness. Column chromatography on silica gel in CH_2Cl_2 (eluants CH_2Cl_2–MeOH, 100:1 and 50:1) afforded two components (R_F 0.37 and 0.28). The fraction (R_F 0.37) was identified as (5*S*)-1-(2,5-dideoxy-5-iodo-β-D-*threo*-pentofuranosyl)-5,6-dihydrothymine (**2**) (290 mg, 25%), m.p. 119 °C (decomp.) (from CH_2Cl_2), $[\alpha]_D^{23}$ −43° (*c* 1 in MeOH) (Found: C, 34.15; H, 4.4;

N, 7.85. $C_{10}H_{15}IN_2O_4$ requires C, 33.9; H, 4.25; N, 7.9%); $\nu_{max.}$ 3 364br, 3 209br, 3 074, 2 936, 1 729, 1 709, 1 694, 1 660, 1 190br, 1 102, 1 045br, 1 031sh, and 1 017 cm^{-1}; δ_H([$^2H_6$]-Me_2SO) 10.17 (1 H, br s, NH), 6.02 (1 H, dd, *J* 8.7, 4.0 Hz, 1′-H), 5.35 (1 H, d, *J* 3.9 Hz, 3′-OH), 4.39—4.14 (1 H, m, 3′-H), 4.0—3.57 (2 H, m, 4′-H and 5′-H_a), 3.44—2.90 (3 H, m, 5′-H_b) and 6-H_2), 2.74—2.28 (2 H, m, 5-H and 2′-H_a), 1.81 (1 H, dd, *J* 14.4, 4.0 Hz, 2′-H_b), and 1.07 (3 H, d, *J* 6.8 Hz, 5-CH_3).

The fraction (R_F 0.28) was identified as (5*S*)-1-(2,5-dideoxy-5-iodo-α-D-*threo*-pentofuranosyl)-5,6-dihydrothymine (**3**) (528 mg, 46%), m.p. 112 °C (decomp.) (from CH_2Cl_2), $[\alpha]_D^{24}$ +14° (*c* 1 in MeOH) (Found: C, 34.1; H, 4.55; N, 7.9. $C_{10}H_{15}IN_2O_4$ requires C, 33.9; H, 4.25; N, 7.9%); $\nu_{max.}$ 3 440, 3 245, 3 102br, 2 928, 1 710br, 1 692br, 1 178, 1 145, 1 090, 1 032, and 1 003 cm^{-1}; δ_H([$^2H_6$]Me_2SO): 10.19 (1 H, br s, NH), 6.19 (1 H, dd, *J* 8.7, 6.6 Hz, 1′-H), 5.24 (1 H, d, *J* 4.6 Hz, 3′-OH), 4.43—4.17 (2 H, m, 3′-H and 4′-H), 3.05 (1 H, dd, *J* 12.0, 10.5 Hz, 6-H_b), 2.71—2.28 (1 H, m, 5-H), 2.18—1.81 (2 H, m, 2′-H_2), and 1.08 (3 H, d, *J* 6.8 Hz, 5-CH_3).

Preparation of (5S)-1-(3,5-*Anhydro*-2-*deoxy*-β-D-threo-*pentofuranosyl*)-5,6-*dihydrothymine* (**1**) *by Cyclization of the* β-5′-*Iodo Anomer* (**2**).—Silver acetate (81 mg, 0.49 mmol) was added to a solution of the β-5′-iodo compound (**2**) (50 mg, 0.14 mmol) in anhydrous MeOH (25 ml) and the mixture heated under reflux for 4 h. It was then filtered and the filtrate saturated with hydrogen sulphide to give a precipitate which was filtered off through a short Celite column. The eluant was evaporated to dryness. Preparative t.l.c. (CH_2Cl_2–MeOH, 10:1; recovery with acetone) gave starting material (20 mg), R_F 0.37, and compound (**1**) (15 mg, 47%), R_F 0.48, identical (mixed m.p., i.r., and ^1H n.m.r. spectra) with an authentic sample.[1]

Preparation of (5S)-1-(3,5-*Anhydro*-2-*deoxy*-α-D-threo-*pentofuranosyl*)-5,6-*dihydrothymine* (**4**) *by Cyclization of the* α-5′-*Iodo Anomer* (**3**).—A solution of the α-5′-iodo compound (**3**) (80 mg, 0.23 mmol) in anhydrous MeOH (33 ml) was treated with silver acetate (133 mg, 0.79 mmol) and after 1.5 h worked up as described for compound (**1**). Preparative t.l.c. (CH_2Cl_2–MeOH, 10:1; recovery with acetone) gave starting material (30 mg), R_F 0.28, and compound (**4**) (30 mg, 59%), R_F 0.44, m.p. 77—78 °C (from acetone–hexane), $[\alpha]_D^{28}$ +6° (*c* 1 in acetone) (Found: C, 52.9; H, 6.5; N, 12.4. $C_{10}H_{14}N_2O_4$ requires C, 53.1; H, 6.25; N, 12.4%); $\nu_{max.}$ 3 435br, 3 200br, 3 100, 2 948, 1 748, 1 690, 1 188, and 1 097 cm^{-1}; δ_H 8.10 (1 H, br s, NH), 6.70 (1 H, dd, *J* 9.2, 5.3 Hz, 1′-H), 5.48 (1 H, t, *J* 4.6 Hz, 3′-H), 5.14—4.94 (1 H, m, 4′-H), 4.82 (1 H, dd, *J* 8.0, 4.6 Hz, 5′-H_a), 4.47 (1 H, dd, *J* 8.0, 2.7 Hz, 5′-H_b), 3.49 (1 H, dd, *J* 11.5, 5.6 Hz, 6-H_a), 3.04 (1 H, dd, *J* 11.5, 11.5 Hz, 6-H_b), 2.92—2.48 (1 H, m, 5-H), 2.33 (1 H, dd, *J* 14.1, 5.3 Hz, 2′-H_a), 1.68 (1 H, ddd, *J* 14.1, 9.2, 4.6 Hz, 2′-H_b), and 1.25 (3 H, d, *J* 6.6 Hz, 5-CH_3).

Transformation of (5S)-1-(3,5-*Anhydro*-2-*deoxy*-α-D-threo-*pentofuranosyl*)-5,6-*dihydrothymine* (**4**) *into the Anomeric* (5S)-5′-*Iodo Derivatives* (**2**) *and* (**3**).—A solution of the α-3′,5′-anhydro compound (**4**) (30 mg, 0.13 mmol) in butan-2-one (2.5 ml) and acetic acid (0.17 ml) was treated with sodium iodide (52 mg, 0.35 mmol) and worked up as described for the transformation of compound (**1**). Preparative t.l.c. (CH_2Cl_2–MeOH, 20:1; recovery with acetone) yielded the β-5′-iodo anomer (**2**) (12 mg, 26%) and the α-5′-iodo anomer (**3**) (20 mg, 43%), identical (mixed m.p., i.r., and ^1H n.m.r. spectra) with those obtained from the transformation of compound (**1**).

(5S)-1-(2,5-*Dideoxy*-β-D-threo-*pentofuranosyl*)-5,6-*dihydrothymine* (**5**).—10% Pd/C (147 mg) was added to a solution of the β-5′-iodo compound (**2**) (147 mg, 0.42 mmol) in 50% EtOH (22 ml) and the mixture was stirred in H_2 atmosphere under 0.10 MPa at room temperature for 4 h. The catalyst was filtered off and the filtrate treated with silver carbonate (58 mg). The precipitate was filtered off and the filtrate saturated with hydrogen sulphide. After filtration through a short Celite column, the filtrate was evaporated to dryness. Preparative t.l.c. (CH_2Cl_2–MeOH, 20:1; recovery with acetone) gave the product (**5**) (65 mg, 69%), R_F 0.23, m.p. 139—141 °C (from MeOH–diethyl ether), $[\alpha]_D^{26}$ −56.5° (*c* 1 in acetone) (Found: C, 50.75; H, 7.15; N, 11.75. $C_{10}H_{16}N_2O_4 \cdot \frac{1}{2}H_2O$ requires C, 50.6; H, 7.2; N, 11.8%); $\nu_{max.}$ 3 408br, 3 233, 3 028br, 2 978, 1 714sh, and 1 688br cm^{-1}; δ_H 8.24 (1 H, br s, NH), 5.85 (1 H, dd, *J* 9.0, 3.9 Hz, 1′-H), 4.27—3.99 (1 H, m, 3′-H), 3.74 (1 H, dd, *J* 12.9, 5.7 Hz, 6-H_a), 3.25 (1 H, dd, *J* 12.9, 9.8 Hz, 6-H_b), 2.84—2.30 (2 H, m, 5-H and 2′-H_a), 1.98 (1 H, dd, *J* 15.3, 3.9 Hz, 2′-H_b), 1.31 (3 H, d, *J* 6.1 Hz, 4′-CH_3), and 1.25 (3 H, d, *J* 6.8 Hz, 5-CH_3).

(5S)-1-(2,5-*Dideoxy*-α-D-threo-*pentofuranosyl*)-5,6-*dihydrothymine* (**6**).—10% Pd/C (131 mg) was added to a solution of the α-5′-iodo compound (**3**) (131 mg, 0.37 mmol) in 50% EtOH (18 ml) and the procedure described above followed except that a 16 h reduction time was used. Preparative t.l.c. (CH_2Cl_2–MeOH, 10:1; recovery with acetone) afforded the product (**6**) (70 mg, 83%), R_F 0.16, m.p. 147—149 °C (from EtOH), $[\alpha]_D^{27}$ +4° (*c* 1 in acetone) (Found: C, 52.7; H, 7.2; N, 12.15. $C_{10}H_{16}N_2O_4$ requires C, 52.6; H, 7.05; N, 12.3%); $\nu_{max.}$ 3 375br, 3 195br, 3 075br, 2 985, 1 715br, 1 675br, 1 185, 1 161, and 1 057br cm^{-1}; δ_H([$^2H_6$]Me_2SO) 10.14 (1 H, br s, NH), 6.11 (1 H, dd, *J* 8.2, 6.5 Hz, 1′-H), 4.93 (1 H, d, *J* 4.4 Hz, 3′-OH), 4.30—3.76 (2 H, m, 3′-H and 4′-H), 3.04 (1 H, dd, *J* 12.0, 10.0 Hz, 6-H_b), 2.73—2.21 (1 H, m, 5-H), 2.15—1.79 (2 H, m, 2′-H_2), 1.09 (3 H, d, *J* 6.4 Hz, 4′-CH_3), and 1.08 (3 H, d, *J* 6.8 Hz, 5-CH_3).

(5S)-1-(3-O-*Acetyl*-2,5-*dideoxy*-β-D-threo-*pentofuranosyl*)-5,6-*dihydrothymine* (**7**).—(a) Acetic acid anhydride (0.5 ml) was added to a solution of the β-2′,5′-dideoxy compound (**5**) (100 mg, 0.44 mmol) in pyridine (2 ml) and the mixture stirred at room temperature for 16 h. It was then concentrated and co-evaporated with ethanol and toluene under reduced pressure. The resultant residue was purified by preparative t.l.c. (CH_2Cl_2–MeOH, 20:1) to give the title compound (**7**) (102 mg, 86%), R_F 0.51, m.p. 171—172 °C (from MeOH), $[\alpha]_D^{26}$ −62° (*c* 1 in MeOH) (Found: C, 53.3; H, 7.0; N, 10.2. $C_{12}H_{18}N_2O_5$ requires C, 55.3; H, 6.7; N, 10.35%); $\nu_{max.}$ 3 320, 2 995, 2 855, 1 745, 1 719, 1 700, 1 177, 1 150, 1 067, 1 058, and 1 020 cm^{-1}; δ_H 8.59 (1 H, br s, NH), 6.17 (1 H, dd, *J* 8.6, 4.4 Hz, 1′-H), 5.34—5.13 (1 H, m, 3′-H), 3.98 (1 H, ddd, *J* 6.4, 3.7 Hz, 4′-H), 3.52 (1 H, dd, *J* 12.9, 5.9 Hz, 6-H_a), 3.23 (1 H, dd, *J* 12.9, 9.5 Hz, 6-H_b), 2.86—2.46 (2 H, m, 5-H and 2′-H_a), 2.12 (3 H, s, $COCH_3$), 1.86 (1 H, dd, *J* 14.4, 4.4 Hz, 2′-H_b), 1.28 (3 H, d, *J* 6.8 Hz, 5-CH_3), and 1.24 (3 H, d, *J* 6.4 Hz, 4′-CH_3).

(b) 5% Rh/Al_2O_3 (80 mg) was added to a solution of 1-(3-*O*-acetyl-2,5-dideoxy-β-D-*threo*-pentofuranosyl)thymine (**11**) (200 mg, 0.75 mmol) in 50% EtOH (17 ml) and the mixture was stirred under 0.41 MPa of H_2 at room temperature for 48 h. The catalyst was filtered off and the filtrate evaporated to dryness. The resulting residue was triturated with MeOH to give title compound (**7**) (181 mg, 90%), identical (mixed m.p., i.r., and ^1H n.m.r. spectra) with that obtained under (a).

(5S)-1-(3-O-*Acetyl*-2,5-*dideoxy*-α-D-threo-*pentofuranosyl*)-5,6-*dihydrothymine* (**8**).—A solution of the α-2′,5′-dideoxy compound (**6**) (100 mg, 0.44 mmol) in anhydrous pyridine (2 ml) was treated with acetic acid anhydride (0.5 ml) and worked up as for the preparation of compound (**7**). Preparative t.l.c. (CH_2Cl_2–MeOH, 20:1; recovery with ethyl acetate) gave the title product (**8**) (104 mg, 88%), R_F 0.49, m.p. 121—122 °C (from diethyl ether), $[\alpha]_D^{23}$ +70° (*c* 1 in MeOH) (Found: C, 53.5; H, 6.35; N, 10.3. $C_{12}H_{18}N_2O_5$ requires C, 53.3; H, 6.7; N, 10.35%); $\nu_{max.}$ 3 197br, 3 080, 2 995, 2 885, 1 740br, 1 730br, 1 678, 1 185,

1 072, 1 060, 1 042, and 1 019 cm^{-1}; δ_H 8.22 (1 H, br s, NH), 6.23 (1 H, dd, *J* 7.6, 7.0 Hz, 1′-H), 5.37 (1 H, m, 3′-H), 4.39 (1 H, ddd, *J* 6.5, 3.2 Hz, 4′-H), 3.48 (1 H, dd, *J* 11.6, 5.7 Hz, 6-H_a), 3.08 (1 H, dd, *J* 11.6, 10.8 Hz, 6-H_b), 2.88—2.61 (1 H, m, 5-H), 2.37—2.12 (2 H, m, 2-H_2), 2.12 (3 H, s, $COCH_3$), 1.26 (3 H, d, *J* 6.4 Hz, 4′-CH_3), and 1.21 (3 H, d, *J* 6.5 Hz, 5-CH_3).

1-(2,5-*Dideoxy*-β-D-threo-*pentofuranosyl*)*thymine* (**10**).—5% Pd/C (150 mg) and 1M NaOH (0.65 ml) were added to a solution of 1-(2,5-dideoxy-5-iodo-β-D-*threo*-pentofuranosyl)thymine[13] (**9**) (200 mg, 0.57 mmol) in ethanol (30 ml) and the mixture was stirred under 0.1 MPa of H_2 at room temperature for 5 h. The catalyst was filtered off and the filtrate evaporated to dryness. The residue was subjected to preparative t.l.c. (CH_2Cl_2–MeOH 15:1 and 10:1, recovery with MeOH) to give the title product (**10**) (120 mg, 93%), R_F 0.18, m.p. 152—153 °C (from acetone), $[\alpha]_D^{27}$ −15° (*c* 1 in MeOH) (Found: C, 53.05; H, 6.5; N, 12.4. $C_{10}H_{14}N_2O_4$ requires C, 53.1; H, 6.25; N, 12.4%); $\lambda_{max.}$ 264 nm (log ε 4.03); $\lambda_{min.}$ 231 nm (log ε 3.34); $\nu_{max.}$ 3 498, 3 440, 3 170br, 3 040, 1 695br, 1 680br, 1 650, 1 200, 1 120, 1 088, 1 058, and 1 023 cm^{-1}; δ_H([$^2H_6$]Me_2SO) 11.20 (1 H, br s, NH), 7.77 (1 H, d, *J* 1.17 Hz, 6-H), 6.02 (1 H, dd, *J* 8.20, 2.34 Hz, 1′-H), 5.25 (1 H, br s, 3′-OH), 4.12—3.75 (2 H, m, 3′-H and 4′-H), 2.29—1.71 (2 H, m, 2′-H_2), 1.77 (3 H, d, *J* 1.17 Hz, 5-CH_3), and 1.23 (3 H, d, *J* 6.15 Hz, 4′-CH_3).

1-(3-O-*Acetyl*-2,5-*dideoxy*-β-D-threo-*pentofuranosyl*)*thymine* (**11**).—This was prepared from 1-(2,5-dideoxy-β-D-*threo*-pentofuranosyl)thymine (**10**) (660 mg, 2.92 mmol) and acetic acid anhydride (2 ml) in anhydrous pyridine (8 ml) following the procedure described for compound (**7**). Column chromatography on silica gel (CH_2Cl_2–MeOH, 100:1 and 50:1 as eluants) gave the product (**11**) (657 mg, 84%), R_F 0.45, m.p. 147—148 °C (from benzene) $[\alpha]_D^{25}$ −12.5° (*c* 1 in acetone) (Found: C, 53.9; H, 6.2; N, 10.45. $C_{12}H_{16}N_2O_5$ requires C, 53.7; H, 6.0; N, 10.45%); $\lambda_{max.}$ 264 nm (log ε 3.98); $\lambda_{min.}$ 231 nm (log ε 3.27); $\nu_{max.}$ 3 293, 3 080, 2 990, 1 746, 1 720br, 1 690br, 1 669br, 1 187, 1 125, 1 044, and 1 025 cm^{-1}; δ_H 9.96 (1 H, br s, NH), 7.45 (1 H, d, *J* 1.2 Hz, 6-H), 6.20 (1 H, dd, *J* 7.8, 2.7 Hz, 1′-H), 5.32 (1 H, dd, *J* 5.4, 3.3 Hz, 3′-H), 4.19 (1 H, ddd, *J* 6.4, 3.3 Hz, 4′-H), 2.79 (1 H, ddd, *J* 15.6, 7.8, 5.4 Hz, 2′-H), 2.09 (3 H, s, $COCH_3$), 1.96 (3 H, d, *J* 1.2 Hz, 5-CH_3), and 1.36 (3 H, d, *J* 6.4 Hz, 4′-CH_3).

(5S)-1-(3,5-*Di*-O-*acetyl*-2-*deoxy*-β-D-erythro-*pentofuranosyl*)-5,6-*dihydrothymine* (**12**).—(5*S*)-1-(2-Deoxy-β-D-*erythro*-pentofuranosyl)-5,6-dihydrothymine[17] (100 mg, 0.41 mmol) was dissolved in dry pyridine (2 ml) and acetic acid anhydride (0.5 ml) and the mixture stirred at room temperature for 16 h. The mixture was evaporated and the residue then co-evaporated with benzene and ethanol to afford a syrup. Preparative t.l.c. (CH_2Cl_2–MeOH, 20:1; recovery with ethyl acetate) afforded the foamy product (**12**) (120 mg, 89%), R_F 0.54, $[\alpha]_D^{27}$ −22° (*c* 1 in acetone) (Found: C, 51.1; H, 6.35; N, 8.5. $C_{14}H_{20}N_2O_7$ requires C, 51.2; H, 6.15; N, 8.5%); $\nu_{max.}$ 3 211br, 2 965, 2 925, 1 732br, 1 694br, 1 182, 1 089, and 1 048 cm^{-1}; δ_H 8.76 (1 H, br s, NH), 6.36 (1H, dd, *J* 7.6, 7.0 Hz, 1′-H), 5.12 (1 H, m, 3′-H), 4.32—4.0 (3 H, m, 4′-H and 5′-H_2), 3.40 (1 H, dd, *J* 12.4, 6.2 Hz, 6-H_a), 3.17 (1 H, dd, *J* 12.4, 10.1 Hz, 6-H_b), 2.81—2.51 (1 H, m, 5-H), 2.11 and 2.09 (6 H, 2 s, 2 $COCH_3$), and 1.27 (3 H, d, *J* 7.0 Hz, 5-CH_3).

Anomerization of (5S)-1-(2,5-*Dideoxy*-5-*iodo*-β-D-threo-*pentofuranosyl*)-5,6-*dihydrothymine* (**2**).—The β-anomer (**2**) (100 mg, 0.28 mmol) and sodium iodide (170 mg, 1.13 mmol) were heated under reflux in butan-2-one (6 ml) and acetic acid (0.5 ml) for 2 h. The mixture was evaporated and the residue then co-evaporated with ethanol to dryness under reduced pressure. The residue was partitioned between ethyl acetate and 5% aqueous sodium thiosulphate. The organic layer was dried (Na_2SO_4) and evaporated to dryness to give a mixture of the β- (**2**) and α- (**3**) anomers. Preparative t.l.c. (CH_2Cl_2–MeOH 20:1, recovery with ethyl acetate) separated the β-anomer (**2**) (26 mg, 26%), R_F 0.37, and the α-anomer (**3**) (44 mg, 44%), R_F 0.28.

Anomerization of (5S)-(2,5-*Dideoxy*-5-*iodo*-α-D-threo-*pentofuranosyl*)-5,6-*dihydrothymine* (**3**).—The α-anomer (**3**) (100 mg, 0.28 mmol) and sodium iodide (170 mg, 1.13 mmol) in butan-2-one (6 ml) and acetic acid (0.5 ml) by the procedure described above for compound (**2**) gave the β-anomer (**2**) (25 mg, 25%) and the α-anomer (**3**) (43 mg, 43%).

Anomerization of (5S)-1-(3,5-*Anhydro*-2-*deoxy*-β-D-threo-*pentofuranosyl*)-5,6-*dihydrothymine* (**1**).—The β-anomer (**1**) (50 mg, 0.22 mmol) was treated with Amberlite IR-120 (H^+) (20 mg) in water (2 ml) by the above described procedure to give a mixture of the β- (**1**) and the α- (**4**) anomers in the ratio 15:85 (based on ^1H n.m.r. signal analysis). Flash chromatography (hexane–ethyl acetate 2:1 and 1:1 as the eluants) yielded the β-anomer (6 mg, 12%), R_F 0.48, and the α-anomer (40 mg, 80%), R_F 0.44. Their spectroscopic properties agreed with those of authentic samples.

Anomerization of (5S)-1-(3-O-*Acetyl*-2,5-*dideoxy*-β-D-threo-*pentofuranosyl*)-5,6-*dihydrothymine* (**7**).—The β-anomer (**7**) (80 mg, 0.30 mmol) was treated with Amberlite IR-120 (H^+) (30 mg) in 50% MeOH (2 ml) by the above described procedure, to give a mixture of the β- (**7**) and α- (**8**) anomers in the ratio 73:27 (based on ^1H n.m.r. signal analysis).

Anomerization of (5S)-1-(3,5-*Di*-O-*acetyl*-2-*deoxy*-β-D-erythro-*pentofuranosyl*)-5,6-*dihydrothymine* (**12**).—The β-anomer (**12**) (200 mg, 0.61 mmol) and sodium iodide (312 mg, 2.08 mmol) in butan-2-one (12 ml) and acetic acid (1 ml) were heated under reflux for 2 h and worked up as for the transformation of compound (**1**). The residue was passed through a silica gel column with CH_2Cl_2. Elution with CH_2Cl_2–MeOH (100:1) afforded the β-anomer (**12**) (112 mg, 56%) at R_F 0.54, identical (i.r. and ^1H n.m.r. spectra) with an authentic sample and at R_F 0.49 a compound identified as (5*S*)-1-(3,5-di-*O*-acetyl-2-deoxy-α-D-*erythro*-pentofuranosyl)-5,6-dihydrothymine (**13**) (72 mg, 36%); an amorphous solid (from diethyl ether–hexane), $[\alpha]_D^{27}$ +28° (*c* 1 in acetone) (Found: C, 51.35; H, 6.35; N, 8.45. $C_{14}H_{20}N_2O_7$ requires C, 51.2; H, 6.15; N, 8.55%); $\nu_{max.}$ 3 198br, 3 063br, 2 926, 1 736br, 1 720sh, 1 686br, 1 161, 1 071, and 1 021 cm^{-1}; δ_H 8.22 (1 H, br s, NH), 6.30 (1 H, dd, *J* 7.6, 5.3 Hz, 1′-H), 5.18 (1 H, m, 3′-H), 4.36 (1 H, m, 4′-H), 4.14 (2 H, m, 5′-H_2), 3.62 (1 H, dd, *J* 11.9, 5.7 Hz, 6-H_a), 3.09 (1 H, dd, *J* 11.9, 10.8 Hz, 6-H_b), 2.95—2.50 (1 H, m, 5-H), 2.11 and 2.10 (6 H, 2 s, 2 $COCH_3$), and 1.27 (3 H, d, *J* 6.7 Hz, 5-CH_3).

Anomerization of (5S)-1-(3,5-*Di*-O-*acetyl*-2-*deoxy*-α-D-erythro-*pentofuranosyl*)-5,6-*dihydrothymine* (**13**).—The α-anomer (**13**) (100 mg, 0.30 mmol) and sodium iodide (156 mg, 1.04 mmol) in butan-2-one (6 ml) and acetic acid (0.5 ml) by the procedure given for compound (**12**), gave a mixture of the β-(**12**) and α- (**13**) anomers. Preparative t.l.c. (CH_2Cl_2–MeOH, 30:1, three developments; recovery with EtOAc) separated the β-anomer (**12**) (55 mg, 55%) and the α-anomer (**13**) (35 mg, 35%), identical (i.r. and ^1H n.m.r. spectra) with those obtained from the anomerization of compound (**12**).

Anomerization of (5S)-1-(2,5-*Dideoxy*-5-*iodo*-β-D-erythro-*pentofuranosyl*)-5,6-*dihydrothymine*[1] (**14**).—The β-anomer (**14**) (100 mg, 0.28 mmol) was treated with sodium iodide (170 mg, 1.13 mmol) in butan-2-one (6 ml) and acetic acid (0.5 ml) and worked up as described for the anomerization of compound

(**12**). Preparative t.l.c. (CH_2Cl_2–MeOH, 20:1; recovery with ethyl acetate) afforded the β-anomer (**14**) (53 mg, 53%) at R_F 0.21, $[\alpha]_D^{19}$ −7.5° (*c* 1 in DMSO) identical (i.r. and ^1H n.m.r. spectra) with an authentic sample and at R_F 0.29 a compound identified as (5*S*)-1-(2,5-dideoxy-5-iodo-α-D-*erythro*-pentofuranosyl)-5,6-dihydrothymine (**15**) (35 mg, 35%), $[\alpha]_D^{27}$ +4° (*c* 1, Me_2SO) (Found: C, 34.15; H, 4.55; N, 8.1. $C_{10}H_{15}IN_2O_4$ requires C, 33.9; H, 4.25; N, 7.9%); $\nu_{max.}$ 3 405br, 3 213br, 3 063, 2 955, 2 913, 1 723br, 1 688br, 1 166, 1 075br, 1 046, and 1 023 cm^{-1}; $\delta_H([^2H_6]Me_2SO)$ 9.99 (1 H, br s, NH), 6.11 (1 H, dd, *J* 7.3, 6.5 Hz, 1′-H), 5.33 (1 H, d, *J* 4.1 Hz, 3′-OH), 4.13 (1 H, m, 3′-H), 3.91 (1 H, m, 4′-H), 3.61 (1 H, dd, *J* 12.3, 5.9 Hz, 5′-H_a), 3.46—2.97 (3 H, m, 5′-H_b and 6-H_2), 2.80—2.31 (2 H, m, 5-H, 2′-H_a), 2.05—1.72 (1 H, m, 2′-H_b), and 1.14 (3 H, d, *J* 7.0 Hz, 5-CH_3).

References

1 V. Škarić, M. Pavela-Vrančič, and J. Matulić-Adamić, *Croat. Chem. Acta*, 1984, **57**, 415.
2 V. Škarić and J. Matulić-Adamić, *Helv. Chim. Acta*, 1983, **66**, 687.
3 H. Ide, R. J. Melamede, and S. S. Wallace, *Biochemistry*, 1987, **26**, 964.
4 R. A. Jacobson and J. Bonner, *Biochem. Biophys. Res. Commun.*, 1968, **33**, 716.
5 T. Kalman, *Ann. N.Y. Acad. Sci.*, 1975, **255**, 326.
6 V. Škarić, D. Katalenić, I. Salaj, and D. Škarić, *J. Chem. Soc., Perkin Trans. 1*, 1982, 2091.
7 V. Škarić, M. Hohnjec, and D. Škarić, *Helv. Chim. Acta*, 1976, **59**, 2972.
8 V. Škarić and J. Matulić-Adamić, *J. Chem. Soc., Perkin Trans. 1*, 1985, 779.
9 K. Kikugawa and M. Ichino, *J. Org. Chem.*, 1972, **37**, 284.
10 H. O. Kalinowski, S. Berger, and S. Brown, ('^{13}C-Spektroskopie,' G. Thieme, Stuttgart, 1984.
11 V. Škarić, J. Matulić-Adamić, and D. Škarić, *Heterocycles*, 1977, **7**, 179.
12 J. P. Horwitz, J. Chua, and M. Noel, *J. Org. Chem.*, 1964, **29**, 2076.
13 J. P. Horwitz, J. Chua, J. A. Urbanski, and M. Noel, *J. Org. Chem.*, 1963, **28**, 942.
14 J. Cadet and R. Teoule, *Carbohydr. Res.*, 1973, **29**, 345.
15 J. A. Kelley, J. S. Driscoll, J. J. McCormack, J. S. Roth, and V. E. Marquez, *J. Med. Chem.*, 1986, **29**, 2351.
16 F. Seela, S. Menkhoff, and S. Behrendt, *J. Chem. Soc., Perkin Trans. 1*, 1986, 525.
17 Y. Kondo and B. Witkop, *J. Am. Chem. Soc.*, 1968, **90**, 764.

Received 28*th January* 1988; *Paper* 8/00324F